REMARKS

Claims 1-18 are pending.

1. Oath/Declaration Informalities:

Examiner, after reviewing the present application, has discovered the oath or declaration is defective. A new oath/declaration will be submitted concurrently with the submission of this response which complies with the requirements of 37 C.F.R. §1.67(a). Specifically, the oath/declaration will clearly identify this application by application number and filing date, as well as properly claim benefit of the parent U.S. Application Serial No. 09/753,814. Applicant respectfully submits this informality will be remedied by the submission of this new oath/declaration in compliance with 37 C.F.R. §1.67(a).

2. Specification Informality:

Examiner has found that the specification fails to reference the related priority applications. Applicant has cured such informality by way of amendment. Applicant is thankful for Examiner's helpful suggestions relating to the necessary corrections. Pursuant to the prescribed requirements under 35 U.S.C. §120 and 37 C.F.R. §1.121, Applicant respectfully asserts that Examiner's requirements have been met.

Additionally, pursuant to Applicant's teleconference with Examiner, no petition is needed under 37 C.F.R. §1.78(a). Similarly, no surcharge is required under 37 C.F.R. §1.17(t), as reference to the prior application was

previously submitted within the time period set forth under 37 C.F.R. §1.78(a). The priority reference was noted in the oath/declaration submitted concurrently with the filing of the present application on July 3, 2003.

In order to comply with the remainder of the 37 C.F.R. §1.78(a) requirements, Applicant is submitting the reference by way of amendment to the first sentence of the specification. Accordingly, Applicant respectfully submits the present application is now in compliance with the previous informalities noted by Examiner.

3. Claim Objections:

Examiner has objected to the form of pending claims 1-18 as being informal, namely due to use of the parenthetical expressions (GVHD) and (HVGD). Additionally, Applicant has cured minor spelling informalities with the current amendments to the claims. Applicant has cured such defect by way of amendment and respectfully requests Examiner withdraw the objection of record with respect to claims 1-18.

4. Rejection under 35 U.S.C. §112, 1st Paragraph:

Claims 1, 2, 7-11 and 16-18 are rejected under §112, 1st paragraph. Examiner maintains the rejection based on the allegations that the specification does not reasonably provide enablement for host-versus-graft disease affecting organs other than the intestine and liver.

In the interests of expediting prosecution, Applicant has amended independent claim 1 to read on treatment of tissues relating to intestine and liver.

In light of the present amendments to the claims, Applicant respectfully requests Examiner withdraw the §112, 1st rejection.

5. Rejection under 35 U.S.C. §103: McDonald et al.

Examiner rejects claims 1-10 and 12-17 as being obvious in view of McDonald et al. Applicant respectfully submits this rejection is in error, for the reasons set forth below, and respectfully requests Examiner withdraw the rejection.

Beclomethasone dipropionate has been used for more than 40 years for the treatment of asthma and lung inflammation conditions. However, the use of this topical active corticosteroid for the treatment of GvHD and the mechanisms behind its action is only now being investigated.

Examiner is of the belief that at the time of the McDonald reference, it would have been obvious to one skilled in the art to orally administer BDP alone or with prednisone over the long term (ie. 29-56 days). Applicant respectfully asserts that this is not the case and, in fact, there is ample evidence to show that at the time, it would have run counter to the prevailing mindset of those skilled in the art to administer topically active

corticosteroids over a course of treatment longer than four weeks.

Even as early as the 1950's, it was known that corticosteroids were involved in the suppression of the adrenal cortex. (Christy et al., Comparative effects of prednisone and of cortisone in suppressing the response of the adrenal cortex to exogenous adrenocorticotropin. *J. Clin. Endocrinol. Metab.* 1956; 16: 1059)

Much of the work involving beclomethasone was performed in asthmatic patients in an effort to improve pulmonary functions within the lungs. (See Utiger, RD, Differences between inhaled and oral glucocorticoid therapy. *N. Engl. J. Med.* 1993; 329: 1731)

In fact, researchers before the time of McDonald et al. knew of the adrenocortical suppression following treatment with beclomethasone. (Prahl, P. Adrenocortical suppression following treatment with beclomethasone and budesonide. *Clin. Exp. Allergy* 1991; 21: 145) It was known to one skilled in the art that treatment involving a regimen of beclomethasone must be weighed against the known suppression of the adrenal axis in the patient. The prevailing view, based on the above references, was to treat the patients for no longer than four weeks. Prahl describes a study which measured the effects of beclomethasone during a six week period, but that study was done in an effort to gauge the profound effects of a longer course of corticosteroid treatment. The Prahl study concluded that when children are treated with beclomethasone or budesonide, their cortisol levels should

be measured and if found to be below a certain level, beclomethasone should no longer be used.

This is strong evidence that those in the field at the time of McDonald et al. knew of the negative effects on the pituitary-adrenal axis in patients which were to be treated with beclomethasone. In fact, the McDonald study only carried treatment out to four weeks and ended the course of beclomethasone delivery at 30 days. This was due to the fact that it was well known at that time that a longer treatment regimen of beclomethasone would put the patients in jeopardy based on the evidence of side effects to adrenal axis function.

A reference is considered to "teach away" from the present invention if that prior art teaching "would likely discourage the art worker from attempting the substitution suggested by the [inventor]." (*Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 724, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990) This is precisely the case in the present application, where McDonald et al. teaches away from the claims of the present invention in that it would not have been obvious to extend the term of treatment. The evidence at the time of McDonald et al. suggested halting treatment with beclomethasone at four weeks and nothing in McDonald et al. or any other reference proffered by Examiner suggests anything to the contrary. As McDonald et al. teaches away from that claimed in the present application, Applicant respectfully requests Examiner withdraw the §103 rejection as applied to this reference.

6. Rejection under 35 U.S.C. §103: Baehr et al.

Examiner has rejected claims 1-10 and 12-17 over Baehr et al. for essentially the same reasons as described above. Specifically, while Baehr et al. does not explicitly disclose the long term therapy of the claimed invention, Examiner believes it would have been obvious to one skilled in the art to orally administer BDP alone or with prednisone for longer than 30 days.

As discussed above, Examiner cannot presume such obviousness. It is apparent, given the amount of evidence which teaches away from the present application, one skilled in the art at the time would not have extended beclomethasone therapy to a "long term" therapeutic regimen, given the negative consequences on the adrenal axis function for an extended period of time. It is not mere coincidence that many of the studies in the prior art only carry out treatment to day 30. It suggests the prevailing thought of those skilled in the art and a conscious awareness of the negative effects on long term use of beclomethasone on the pituitary-adrenal axis in a patient in need of such therapy. As Baehr et al. points out, even though BDP acts topically rather than systemically, "[w]e cannot rule out a systemic effect, however, as the data do show an overall suppression of the adrenal axis that serves as indirect evidence for systemic absorption of BDP." (See Baehr et al., page 1236-1237) Investigators at the time of Baehr et al. were obviously aware of the negative effects of beclomethasone treatment and, therefore, controlled the dosing and the length of treatment accordingly. It would not have been obvious to

one skilled in the art at the time of Baehr to extend treatment beyond the 30 day benchmark, as the risk to the adrenal axis would likely be to great to contemplate extended treatment.

Applicant respectfully asserts that rejection over Baehr et al. has been obviated and requests Examiner withdraw the corresponding §103 rejection.

7. Rejection under 35 U.S.C. §103: McDonald et al., Baehr et al. in view of Lundquist (US 5,843,465), Brancq et al. (US 5,958,431) or Benita et al. (US 6,007,826)

Claim 11 is rejected under §103 as being unpatentable over the combination of the above mentioned references.

As discussed above, the McDonald et al. and Baehr et al. references teach away from that proposed in the present invention. The present invention as claimed describes a method of long term treatment using beclomethasone. The cited art teach away from such a proposition due to the then-current evidence of limiting dose/length of treatment using beclomethasone due to the described problems associated with the treatment on the adrenal axis of patients.

Applicant respectfully requests withdrawal of the §103 rejection as applied to claim 11, as the combination of references would be improper in light of the above arguments.

8. Rejection under 35 U.S.C. §103: Punch et al., Chao, Sequeira et al. (6,057,307)

Claims 1-16 and 18 are rejected under §103 as being unpatentable over Punch et al. or alternatively Chao, in view of Sequeira et al.

A combination of references to meet the requirements under §103 is proper if the combination teaches or suggests all of the claimed limitations of the present invention. MPEP §2143.03. Applicant respectfully asserts this requirement is not met in this case, rendering the §103 rejection improper.

The combination of Punch et al., Chao and Sequeira et al. must suggest the following limitations:

1) A patient requiring long term therapy;
2) Patient having undergone hematopoietic cell transplantation;
3) Patient having GVHD; or
4) Patient having undergone organ allograft transplantation;
5) Patient having HVGD;
6) Method of treatment comprising long term topical oral administration of a topically active corticosteroid
7) Treatment directed to intestine or liver tissues.

Examiner recognizes the fact that neither Punch et al. nor Chao refer to topical administration of corticosteroids. Nor do the references discuss the directed treatment to intestine or liver tissues.

Sequeira et al. does not remedy the deficiencies of Punch et al. and Chao in combining to form a proper rejection under §103. Sequeira et al. describes a method of treating a corticosteroid responsive disease of the lower airway passages or lungs. As the claims of the present invention are now directed to treatment of intestine or liver tissues, Sequeira et al. fails to complete the requirements of a proper combination of references under §103. There would be no suggestion or motivation for one skilled in the art to apply the teachings of Sequeira et al. to the present invention.

Nothing in the art at the time would have suggested that topically administering mometasone furoate to the lungs would yield the same results as topically administering same to intestine or liver tissues. Furthermore, the combination of references fails to teach or suggest all of the claimed limitations of the present invention. There is no suggestion of topical administration of corticosteroids in a treatment regimen directed to intestine or liver tissues. Based on the present amendments to the claims and the above arguments, Applicant respectfully requests Examiner withdraw the §103 rejection as improper.

9. Double Patenting

Claims 1-18 are rejected for obviousness-type double patenting as being unpatentable over US Patent No. 6,096,731 ("'731").

Applicant respectfully asserts that this rejection is in error, as the claims of the present invention are directed towards long term treatment. The '731 patent is directed towards prevention of the disease and sets out specific criteria on when the corticosteroid is to be administered to the patient. Furthermore, there is no suggestion in the '731 specification that long term therapy would be beneficial at all, which would be a required showing given the discussions above regarding the knowledge of one skilled in the art of the adrenal axis suppression observed in treating for longer than 30 days.

Applicant respectfully requests withdrawal of the above- identified rejections and allowance of the present application based on Applicant's arguments and amendments. It is believed that this response is timely filed along with the appropriate fees for a one-month extension of time. If there are other fees due, Commissioner is authorized to draw them from Deposit Account 502-235. If there are any questions or comments, Applicant's attorney may be reached at the telephone number state below.

Respectfully submitted,

Dated: August 25, 2006

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